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Editorial

Takotsubo syndrome: From a reversible to a chronic condition in search for the Ariadne's ball of string

Takotsubo syndrome (TTS), originally named because of the shape that the left ventricle takes during the acute phase resembling a Japanese octopus trap, has undergone during the last 20 years a significant revaluation from being considered a form of cardiomyopathy to reversable acute heart failure syndrome [1,2].

An attending physician in the Cardiac Intensive Care Unit might experience a sense of relief and perhaps diminished concern, when realizing that the middle-aged patient exhibiting a hypokinetic left ventricle, has not an extensive myocardial infarction but rather a TTS. This reaction could depend on the physician's belief that, in the case of TTS, the patient's ventricular function will likely return to within normal limits over time. Regrettably, it has become increasingly more evident that this condition is not as reversible as once thought, and it might be more complex than this hopeful outlook suggests [3,4].

In fact, emerging data, underscore that TTS leads to adverse cardiovascular events that extend beyond the acute phase (Fig. 1) [3–7]. Jensen et al., utilizing data from the Danish Nationwide Register, examined a substantial cohort of 890 individuals with TTS [3]. Interestingly during the 90-days follow-up period, there was an increased incidence of cerebrovascular events (2.1%), significantly higher than that of age- and sex-matched background, atrial fibrillation (AF), and myocardial infarction (MI) cohorts (0.1, 1.1 and 1.5%, respectively). This prompts speculation about whether left ventricular function remained compromised during the follow-up period leading to thrombus formation, and, eventually, to embolism. Unfortunately, we can only speculate on these mechanisms because the study present limitations, including the absence of information on key factors such as left ventricular ejection fraction and the presence of left ventricular thrombus

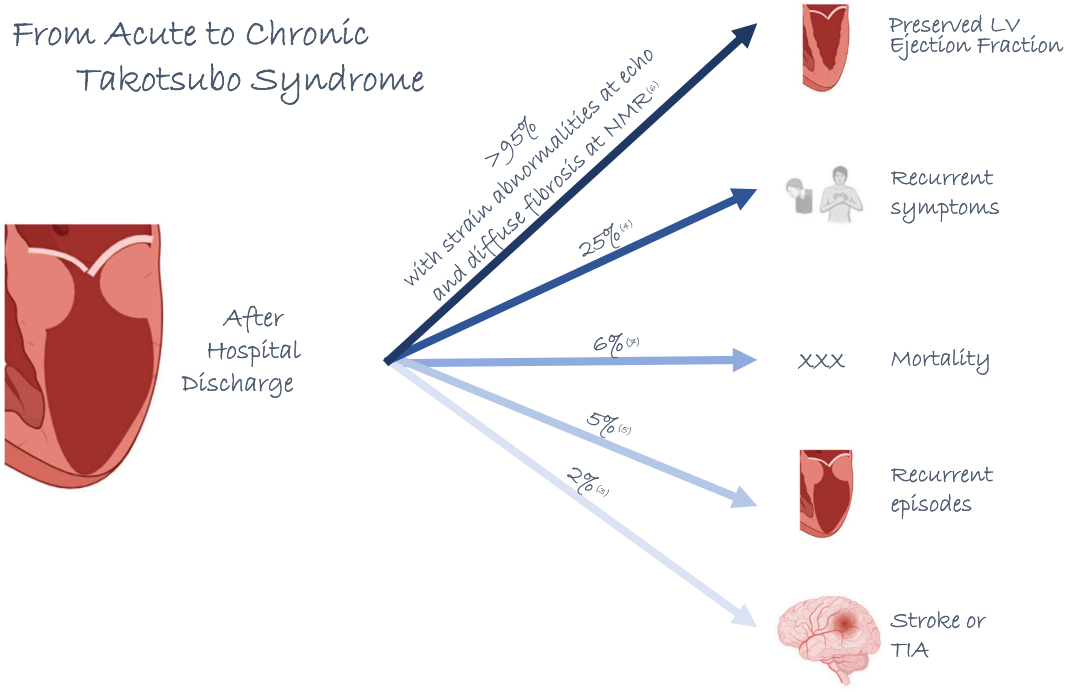

Fig. 1. Outcome of patients with Takotsubo syndrome after hospital discharge. NMR: nuclear magnetic resonance. TIA: transient ischemic attack. References, see text for more details: 3) Jessen N, Int J Cardiol 2023; 4) Parodi G, Chest 2011; 5) Ghadri JR, Eur Heart J 2018; 6) Schwarz K, J Am Soc Echocardiography 2017; 7) Templin C, N Engl J Med 2015.

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and/or embolism during hospitalization, conditions observed in up to 3% of Takotsubo patients [8]. Furthermore, there was a lack of data on anticoagulant therapy after discharge.

In addition, Jensen's data also confirm that TTS is associated with a significant mortality rate after hospital discharge. In fact, the cumulative 90-day mortality in the Takotsubo background AF and MI cohorts, was 5.1%, 0.3%, 1.7% and 5.6%, respectively.

However, Jensen's paper has the strength to reinforce the concept that the initial relief felt by the physician of the above example upon diagnosing TTS, should be tempered by the growing recognition that this condition's impact extends beyond its acute phase (Fig. 1). At moment, no specific comprehensive chronic phase recommendations are available. In this regard, follow up visits timing (including imaging) and related therapeutic interventions depends mainly on clinical patient status. Current medications include ACE inhibitors (or ARB) and beta-blockers, to target "heart failure syndrome". Furthermore, given the residual risk of intracardiac thrombi, the routine use of anticoagulants remains matter of debate to be explored by further research. Thus, a personalized approach appears to be the more appropriate to tailoring disease prevention and treatment.

Basic sciences are crucial to understand and to establish future directions in TTS. Numerous studies have explored TTS through animal models, a method that has sparked debate due to its simplification of the complex human condition. Nonetheless, these models offer valuable insights into the disease's mechanisms and progression [8]. In the acute phase, animal models suggest that chromonar, a selective coronary vasodilator, induces recovering of contractile function in the apex. [9]. In addition, pretreatment with beta-blockers improved survival but did not affect structural and functional alterations in the acute phase of TTS [10]. Thereafter the acute phase, in vivo imaging, histochemistry, protein, and proteomics analyses unveiled an ongoing metabolic shift in the heart towards dysfunctional metabolism. Ultimately, this led to irreparable damage in cardiac function and structure [10]. This model potentially explains why cardiac energetics are significantly diminished in the acute phase of TTS, with some recovery observed by the fourth month. In addition, it points to dysregulation of glucose metabolic pathways as a main cause of long-term cardiac disease and supports early therapeutic management.

Although these studies help in the understanding mechanisms and sequalae of TTS, the complete underlying sequence of events causing decrease global left ventricular systolic function and related acute and chronic complications, remains unknown. In this regard, it is going to be "conditio sine qua non" to participate to national and international TTS registries in order to implement on a large scale the paradigm "education, research and care".

We aspire to have our own "Ariadne's ball of string" to guide us through the intricate nature of TTS. Furthermore, we hope that the ongoing TTS dilemma will continue to pique our curiosity. As Professor Bill McKenna once wisely remarked to the first author of this editorial " What we don't understand, doesn't seem interesting".

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